A PHASE I/II TRIAL OF INTRAPROSTATIC INJECTION OF CG 7060 FOLLOWED BY THREE-DIMENSIONAL CONFORMAL RADIATION THERAPY (3D-CRT) IN PATIENTS WITH CLINICALLY LOCALIZED INTERMEDIATE OR HIGH-RISK PROSTATE CANCER

SCIENTIFIC ABSTRACT

This study is designed to investigate the use of CG 7060, attenuated, replication-Competent adenovirus (Ad5), which has been modified by the addition of the PSA promoter/enhancer elements to replicate preferentially in cells producing PSA. A previous study evaluated treatment with CG 7060 in 20 patients with locally recurrent prostate cancer following radiation therapy. Patients received 1 of 5 dose levels (1×10^{11} 3×10^{11} 1×10^{12}, 3×10^{12}, and 1×10^{13}). Four patients had a PSA partial response (decline in PSA by 50% without normalization): 2 of 6 at 3×10^{12} and 2 of 5 at 1×10^{13}. There were no serious adverse events. Injection site reaction was the most common adverse event and consisted of local pain, swelling, or bruising, followed by flu-like symptoms such as fever, chills, headache, and weakness. Grade 2 fever was experienced by all patients treated with the 3rd and 4th dose levels. No significant laboratory abnormalities were observed, and abnormalities that did occur quickly resolved to pretreatment levels.

Prostate cancer is currently the most common (noncutaneous) malignant neoplasm and the second leading cause of cancer-specific death among males in the US. The incidence of this disease has increased dramatically over the past 25 years, in part because of better detection with an increase in screening for elevated prostate-specific antigen (PSA). Caught in its earliest stages, prostate cancer has a high cure rate. But at many levels of the disease, an absence of satisfactory treatment continues, and available treatments generally are not curative.

OBJECTIVES

The primary objectives are to determine maximum tolerated dose (MTD) and safety and tolerance of CG 7060 administered intraprostatically when combined with three-dimensional conformal radiation therapy (3D-CRT). Secondary objectives are to determine: PSA decline, PSA nadir, proportion of patients with PSA < 0.5 ng/mL; time to biochemical (PSA) failure; time to clinical progression; bioavailability and biodistribution of CG 7060 combined with 3D-CRT administered intraprostatically; immune response; and rate of positive prostate biopsy at 18 months post-treatment.

PATIENT POPULATION

Up to 34 patients with histologically proven, localized adenocarcinoma of the prostate, who are eligible for 3D-CRT. Only patients at intermediate-risk will be enrolled in the dose-escalation phase of the study and 3 or 4 patients at high-risk may be enrolled at the maximum tolerated dose (MTD).

STUDY DESIGN

Open-label, multicenter, dose-finding study.

TREATMENT PLAN AND SCHEDULE

Following scanning and prostatic volumetric analysis, on study Day 1, patients will receive up to 80 viral deposits of CG 7060 using up to 40 needles, under ultrasonographic guidance and using a transperineal approach via a standard prostatic brachytherapy template. A maximum total volume of 8 mL of virus (after dilution) will be injected into the prostate.

3D-CRT will commence 3 days following instillation of CG 7060 on study Day 4. The dose of 3D-CRT will be 7380 cGy to the planning target volume (PTV). Patients will be treated with 180 cGy daily, 5 days a week, for 41 treatments.

Patients will be participating actively in the study for 20 months. They will be followed weekly during the course of radiation therapy (8 weeks), then monthly for 6 months, then every 3 months for 12 months. At the end of the study, patients will be asked to enroll in a separate long-term follow-up protocol.

DOSE

Patients at intermediate-risk will receive treatment with CG 7060 at one of four dose levels (1, 2, 3, or 4). Each dose level will be evaluated in three patients according to a sequential-group, dose-escalating design. Dose levels 1, 2, and 3 will consist of a single dose of 1×10^{12}, 3×10^{12}, and 1×10^{13} viral particles, respectively. Dose level 4 will consist of 2×10^{13} viral particles administered in two doses of 1×10^{13} viral particles each, 1 month apart. The maximum tolerated dose (MTD) will be evaluated in a total of 20 patients. Three to four patients at high-risk may be enrolled at the MTD.

DOSE-LIMITING TOXICITY

Dose-limiting toxicity is defined as any treatment-related grade 3 or 4 non-hematological toxicity, excluding alopecia, or any NCI Grade 4 hematological toxicity that does not resolve in less than 5 days.

PRODUCT

CG 7060 is an attenuated replication-competent adenovirus (Ad5) that has been genetically modified by the insertion of the human PSA enhancer/promoter elements. The backbone of the viral DNA is the human adenovirus Type 5, with the E3 region deleted. The PSA gene is part of the human kallikrein gene family. The PSA enhancer region contains three androgen response elements (AREs) providing a highly tissue-specific expression pattern for PSA. Insertion of the PSA enhancer and promoter regions upstream of the viral E1A gene thus results in transcriptional control of E1A expression

and tissue-specific replication of this virus in PSA-positive cells (creation of a selectively replicating oncolytic virus). Since only genetic regulatory elements have been added to the virus backbone, no transgene expression occurs from CG 7060.

CG 7060 is supplied as a sterile, frozen liquid in single use pyrogen-free plastic vials containing 0.5 to 3.0 mL of virus at a concentration of 5×10^{11} to 3.3×10^{12} viral particles/ml.